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The Role of B_1 and B_2 Bradykinin Receptors in Inflammatory Pain

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Bradykinin has been recognized for many years as an important inflammatory mediator. Its ability to activate nociceptive afferent nerve terminals of the Aδ and C types (Beck and Handwerker 1974; Lang et al. 1990; Mizumura et al. 1990) and to elicit pain in human subjects when applied to a blister base (Whalley et al. 1989) or injected intradermally (Manning et al. 1991) suggest that it may play a role in the genesis of inflammatory pain. Bradykinin is one of a family of kinins produced by cleavage of precursor protein molecules (kininogens) under conditions of tissue damage in which the proteolytic cascade becomes activated (Proud and Kaplan 1988; Bhoola et al. 1992).

Bradykinin and Lys-bradykinin (kallidin) are formed mainly from plasma and tissue kininogens, respectively. Both are subject to C-terminal cleavage by kininase 1-peptidases, which results in the formation of other biologically active kinins, namely [desArg^9]-bradykinin and [desArg^{10}]-kallidin. These active kinins are converted to inactive products by various peptidases, mainly the kininase 2-peptidases, angiotensin converting enzyme, and neutral endopeptidase (Fig. 1). The enzymes responsible for the kininogen cleavage (kininogenases, often called kallikreins) and the mechanisms by which they become activated are well understood (Proud and Kaplan 1988), but rather little is known about the factors that regulate the activity of the kininase 1-peptidases or the kininase 2-peptidases. To complicate matters further, a kinin variant known as T-kinin occurs in the rat, and another variant, Hyp^3-bradykinin, has been detected in man (Matsumura et al. 1989). Measurements of the concentration of active kinins in the tissues have proved difficult, owing to doubts about the specificity of the antibodies used in radioimmunoassays (Proud and Kaplan 1988; Bhoola et al. 1992), and the

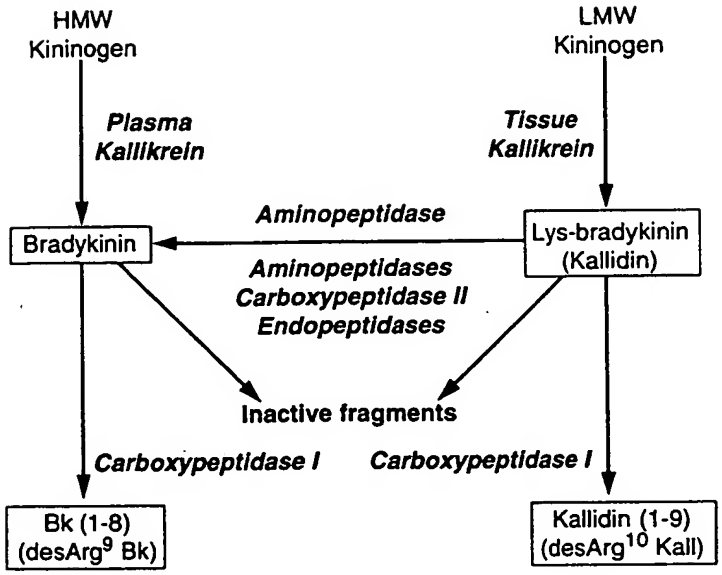

Fig. 1. Formation and interconversion of active kinins (compounds in boxes) from kininogens.

published data are limited (Tissot et al. 1985; Burch and DeHaas 1990; Majima et al. 1993; Decarie et al. 1994). Our current understanding of the role of kinins in pain and nociception thus rests mainly on the effects of kinin receptor antagonists, most of which are peptides that have been developed from the original leads discovered by Stewart (Steranka et al. 1989; Regoli et al. 1993; Stewart 1995).

BRADYKININ RECEPTORS

Two bradykinin receptor subtypes, B_1 and B_2, have been clearly identified, initially from pharmacological evidence (Regoli and Barabe 1988), and confirmed by molecular cloning (McEachern et al. 1991; Ma et al. 1994; Menke et al. 1994; Bachvarov et al. 1996; Chai et al. 1996). The main pharmacological difference lies in the selectivity of the B_1 receptor for peptides lacking the C-terminal arginine residue of bradykinin (i.e., [desArg^9]-bradykinin and [desArg^{10}]-kallidin), whereas the B_2 receptor shows selectivity for the intact peptides. Similarly, antagonist peptides, such as icatibant (HOE140, Hock et al. 1991), that possess an N-terminal arginine residue also show selectivity for the B_2 receptor, while the corresponding [desArg] analogs are B_1-selective.

Tissue Kallikrein

LMW Kininogen

The B_1 and B_2 receptors both belong to the class of G-protein coupled receptors with the conventional architecture comprising a single polypeptide chain with 7 α-helical transmembrane segments. The sequence homology of the two types is, however, quite low (approximately 40%), and the B_1 receptor resembles other peptide (e.g., angiotensin) receptors more closely than it resembles the B_2 receptor. As with other peptide receptors, notably the tachykinins, considerable species differences in the B_1 and B_2 receptor sequences are also reflected in distinct pharmacological differences (Regoli et al. 1993; Regoli et al. 1994). The genomic sequence of the B_2 receptor consists of three or four exons, depending on the species, the largest being the downstream exon (exon 4 in the rat), which contains a start codon plus the whole coding domain for seven transmembrane helices plus the N- and C-terminal domains of the receptor. Expression of this form gives rise to a receptor protein with 30 residues in the extracellular N-terminal domain. There are, however, additional start sequences further upstream in exons 2 and 3 (Fig. 2), and recent evidence suggests that alternative forms and splice variants can indeed be expressed (McIntyre et al. 1993; Park et al. 1994; Pesquero et al. 1994; AbdAlla et al. 1996), the difference being in the length and structure of the extracellular domain. So far, there is no evidence to relate this potential molecular diversity in the B_2 receptor structure to the

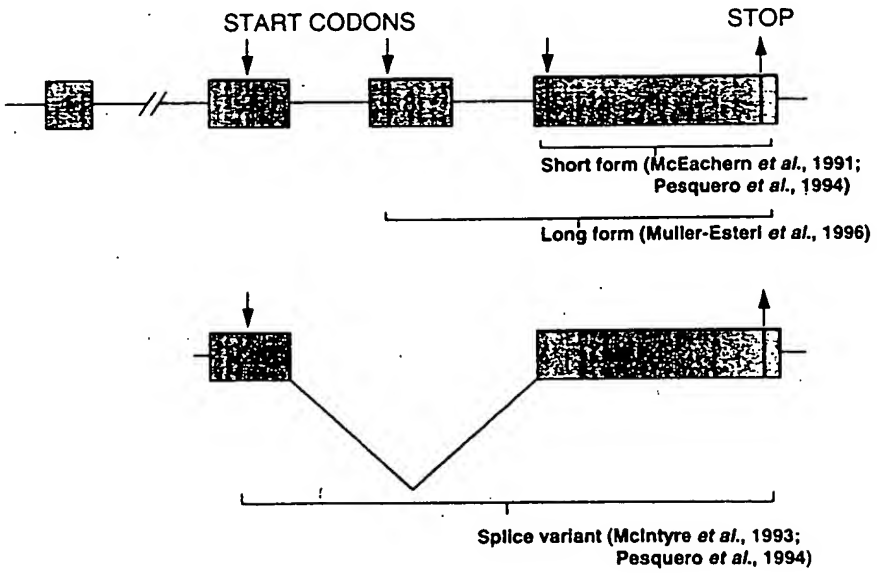

Fig. 2. Gene structure and putative variants (short form, long form, and splice variant form) of the expressed B_2 bradykinin receptor.

pharmacological diversity suggested by various authors (Farmer and Burch 1992; Regoli et al. 1993, 1994), and more work needs to be done on the pharmacological properties of these splice variants. At least four known endogenous kinin mediators interact with a potentially diverse family of receptors, which suggests that the kinin system may operate in a highly complex way of which we have only a fragmentary understanding.

The transduction mechanisms by which B_1 and B_2 receptors mediate their cellular effects appear to be similar and share many pathways in common with other G-protein coupled receptors (see reviews by Farmer and Burch [1992b] and Burch et al. [1988]). Production of inositol phosphates, leading to release of intracellular calcium, occurs through activation of phospholipase C. Production of arachidonic acid, leading to the release of eicosanoids, results from activation of both phospholipase C and phospholipase A_2. The differences between the pathways activated by B_1 and B_2 receptors have been studied mainly in vascular endothelial and smooth muscle cells, which express both types of receptor. Agonists at either receptor cause a rapid and transient rise in $[Ca^{2+}]_i$ due to release of intracellular Ca^{2+} (Marsh and Hill 1994; Smith et al. 1995; Mathis et al. 1996). Activation of B_2 receptors causes a rapid and specific desensitization of the response, which does not occur with B_1 receptor agonists. Furthermore, the transient rise in $[Ca^{2+}]_i$ caused by B_1 (but not B_2) receptor activation is followed by a sustained increase associated with entry of extracellular Ca^{2+}. Calcium channel blocking agents do not in general affect these bradykinin-induced movements of Ca^{2+}, with the exception of nickel, which inhibits the response to B_2, but not B_1 receptor agonists (Smith et al. 1995). B_1 and B_2 receptors both appear to be coupled to phospholipase A_2 and the release of arachidonic acid. In studies on the action of bradykinin on sensory neurons, Burgess et al. (1989) showed that the inward current response of these neurons was due mainly to activation of phospholipase C, which in turn resulted in the formation of inositol phosphates and diacylglycerol. The latter compound is known to activate protein kinase C, and hence to promote phosphorylation of various cellular proteins. Sensory neurons respond by generating an inward (excitatory) current, which accounts for the excitatory effect of bradykinin.

In summary, the effector mechanisms that mediate B_1 and B_2 effects appear to be similar. From a physiological point of view, therefore, it appears that the factors controlling kinin formation (in particular the C-terminal cleavage that results in the formation of B_1 receptor agonists) and receptor expression (in particular the induction of B_1 receptors) are the main determinants of the nature of the tissue response. If the difference in the desensitization kinetics for B_1 and B_2 responses that has been described in vascular cells also applies to other cells involved in tissue reactions to injury, this

difference may also be important as a mechanism favoring involvement of B_1 receptors in long-lasting tissue responses.

ROLE IN PAIN AND NOCICEPTION

Bradykinin, injected into the skin of human subjects (Manning et al. 1991) or applied to a blister base (Whalley 1979; Whalley et al. 1989), evokes a burning pain, which can be inhibited by B_2-receptor antagonists. [DesArg^9]-bradykinin does not elicit such a response. From these findings, which suggest that the activation of nociceptive nerve terminals is mediated by B_2, but not B_1 receptors, it was inferred that only B_2-receptors were likely to play a role in kinin-mediated pain mechanisms. This view was reinforced by several studies in which specific B_2-receptor antagonists, developed from the series of peptide antagonists synthesized by Stewart and his colleagues (Stewart and Vavrek 1989, 1990; Hock et al. 1991), were shown to have analgesic properties in acute antinociceptive models (Steranka et al. 1987; Wirth et al. 1991; Perkins et al. 1993; Griesbacher et al. 1994).

EFFECTS OF BRADYKININ ON SENSORY NEURONS

Bradykinin has a direct excitatory effect, mediated by B_2 receptors, on nociceptive sensory nerve terminals in a wide variety of tissues (Rang et al. 1994). Its excitatory effect in intact tissues is partly inhibited by cyclooxygenase inhibitors, and therefore thought to involve prostanoid release, as various prostaglandins also cause nociceptor activation or sensitization (Birrell et al. 1993; Kumazawa et al. 1993; Rueff and Dray 1993). B_2 receptors are present on sensory neurons (Steranka et al. 1988) and bradykinin exerts a direct excitatory effect on the membrane of sensory neurons, which has been analyzed by recording from isolated dorsal root or nodose ganglion cell bodies in vitro. The excitatory effect is associated with an inward current associated with an increased permeability to cations (Burgess et al. 1989; McGehee et al. 1992; Nicol and Cui 1994). A variety of other membrane changes has also been described (Heapy et al. 1993), notably the suppression of a slow spike after-hyperpolarization. This after-hyperpolarization results from the opening of calcium-activated K-channels (Weinreich 1986; Weinreich et al. 1995) and normally limits the ability of the cell to fire repetitively. Blocking it thus allows the cell to fire a train of impulses in response to a depolarizing current. This phenomenon is well documented for visceral afferent cell bodies in the nodose ganglion but is probably of less importance for somatic sensory neurons, the cell bodies of

which show only very small calcium-activated potassium currents (Naruse et al. 1992).

In general, the excitatory effects of bradykinin are rather transient, due mainly to the rapid desensitization that occurs. As well as causing direct excitation, however, bradykinin also sensitizes nociceptive terminals to thermal and mechanical stimuli, and this effect appears to be more persistent (Neugebauer et al. 1989; Koltzenburg et al. 1992; Birrell and McQueen 1993) and may be functionally more important in accounting for the role of bradykinin in the genesis of inflammatory hyperalgesia. Several studies have shown that bradykinin causes thermal hyperalgesia, based on subjective pain ratings in humans (Manning et al. 1991), behavioral tests in rats (Schuligoi et al. 1994), or recording of afferent discharges (Koltzenburg et al. 1992) (see also reviews by Kress and Reeh 1996; Kumazawa 1996). The work of Kumazawa's group on the response of dog testicular nociceptors suggests that thermal sensitization may result from an increase in intracellular cyclic adenosine monophosphate (cAMP) (Mizumura et al. 1993, 1994; Kumazawa et al. 1994), secondary to activation of prostanoid or histamine receptors; the inhibition of the effect of bradykinin by cyclooxygenase inhibitors such as indomethacin is consistent with this interpretation.

The recent studies of Cesare and McNaughton (1996) are of interest in this context. They showed that a subpopulation of dorsal root ganglion cell neurons in tissue culture responded to heating in the noxious range (42–50°C) with a sustained inward current. The same cells gave a transient inward current response to application of bradykinin, after which the response to heating was significantly increased. As was found for the excitatory effects reported by Burgess et al. (1989), the sensitization produced by bradykinin was mimicked by treatment with phorbol esters and blocked by addition of staurosporine, an inhibitor of protein kinase C, so it was suggested that protein phosphorylation, resulting from activation of protein kinase C, was responsible for the heat sensitization. Sensitization to repeated heat stimuli has been reported in studies of nociceptor discharge in intact tissues, such as skin, cornea, and testis (Kress and Reeh 1996; Kumazawa 1996), where a possible explanation would be the release of sensitizing mediators. The experimental findings of Cesare and McNaughton suggest that bradykinin could well play a part in this mechanism, though the key experiment of testing whether such sensitization of nociceptive nerve terminals in situ is prevented by bradykinin antagonists has not yet been reported.

In contrast to B_2 receptors, B_1 receptors do not appear to be expressed by sensory neurons either under normal conditions or in the presence of tissue inflammation (Davis et al. 1996), and specific B_1 receptor agonists fail to cause excitation of nociceptive nerve terminals.

B_1 RECEPTORS IN EXPERIMENTAL PAIN MODELS

The evidence discussed above suggests that the direct effects of bradykinin on sensory neuron function are mediated exclusively via B_2 receptors. However, a substantial body of evidence now implicates B_1 receptors in the pathophysiology of inflammatory pain and hyperalgesia (Dray and Perkins 1993). In simple inflammatory models such as adjuvant-induced monarthritis or UV-induced skin inflammation, which are associated with mechanical and thermal hyperalgesia, B_1 receptor antagonists such as [desArg^9, Leu^8]-bradykinin were more effective than the B_2 receptor antagonist HOE140 in reversing the hyperalgesia (Perkins et al. 1993). Correspondingly, local injection of [desArg^9]-bradykinin into inflamed joints caused a marked hyperalgesia, whereas this reaction did not occur in noninflamed joints (Davis and Perkins 1994a; Fig. 3). B_1 receptor activation also contributed to the increased vascular permeability of the synovial vessels in inflamed joints (Cruwys et al. 1994). These findings show that inflammation is accompanied by an increase in the contribution of B_1 receptors to the control of

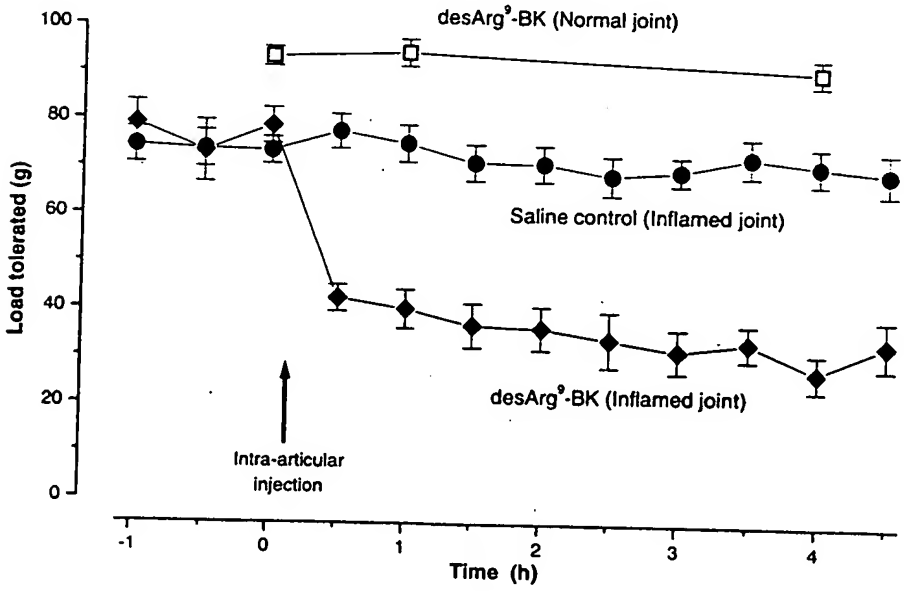

Fig. 3. Hyperalgesia induced by injection of [desArg^9]-bradykinin into the inflamed knee joint of the rat. Reduction of the load tolerated is indicative of hyperalgesia. Injection of [desArg^9]-bradykinin (50 pmol in 50 µl saline) into the normal joint has no effect (top curve), whereas the same injection into a joint injected with complete Freund's adjuvant (10 µl, 72 hours previously) causes a marked hyperalgesia lasting for several hours (lower curve). Values plotted are mean ± SEM, n = 8–24 (data from Davis and Perkins 1994a).

nociceptors and vascular permeability, compared with the normal situation, in which kinin effects are mediated largely or entirely through B_2 receptors. This change may well reflect the increased B_1 receptor expression that is known to occur under conditions of inflammation (see Marceau 1995), but other factors may also be involved, such as an increase in the activity of kininase I, leading to increased conversion of bradykinin to [desArg^9]-bradykinin, or migration into the inflamed tissue of cells that constitutively express B_1 receptors.

Recent studies directed toward identifying the factors responsible for the switch from B_2 to B_1 receptors in mediating hyperalgesia under conditions of inflammation suggest that interleukin-1 (IL-1) may play a key role (Davis and Perkins 1994b). Injection of IL-1β, IL-2, or IL-8 into the rat knee joint resulted in a B_1-receptor-mediated hyperalgesia, whereas other cytokines, such as IL-6, IL-8, or TNFα did not have this effect. Because the effects of IL-2 and IL-8 were blocked by the IL-1 receptor antagonist, IL-1ra, it was concluded that IL-1 must be the common path through which these other cytokines act. Although IL-1 injected into the knee joint is quickly disposed of, the resulting hyperalgesia lasts for several hours, and throughout this period systemic administration of either a B_1- or a B_2-receptor antagonist was able to reverse the hyperalgesia (Fig. 4), which showed that bradykinin continued to exert a hyperalgesic effect for several hours after exposure of the tissue to IL-1. Interestingly, the long-lasting effect of IL-1 was prevented if a B_1-receptor antagonist was co-injected with IL-1 into the joint, which implies that the train of events set in motion by IL-1, leading to the bradykinin-mediated hyperalgesia, could be prevented if B_1 receptors were blocked at the outset. In contrast, blocking B_2 receptors did not interfere with the subsequent development of the hyperalgesia (Fig. 4). Thus, B_1 receptors appear to exert a dual role: initially, activation of B_1 receptors plays a part in the subsequent train of events that results in the ongoing kinin-mediated hyperalgesia; later, when the hyperalgesic state is established, ongoing activation of B_1 receptors contributes directly to it. B_2 receptors, however, do not appear to be essential for initiating the train of events leading to the persistent hyperalgesic state, but their ongoing activation contributes directly to it. Indomethacin reverses IL-1-induced hyperalgesia in this model, which suggests that eicosanoid production plays an important role. A recent report (Ahluwalia and Perretti 1996) has provided further evidence for a role for B_1 kinin receptors in inflammation per se. A B_1 receptor antagonist was able to block IL-1β-induced leukocyte accumulation in the mouse, whereas a B_2 antagonist had no effect. Furthermore, 24 hours following IL-1β injection into an air pouch in the mouse, the B_1 receptor agonist, [desArg^9]-bradykinin,

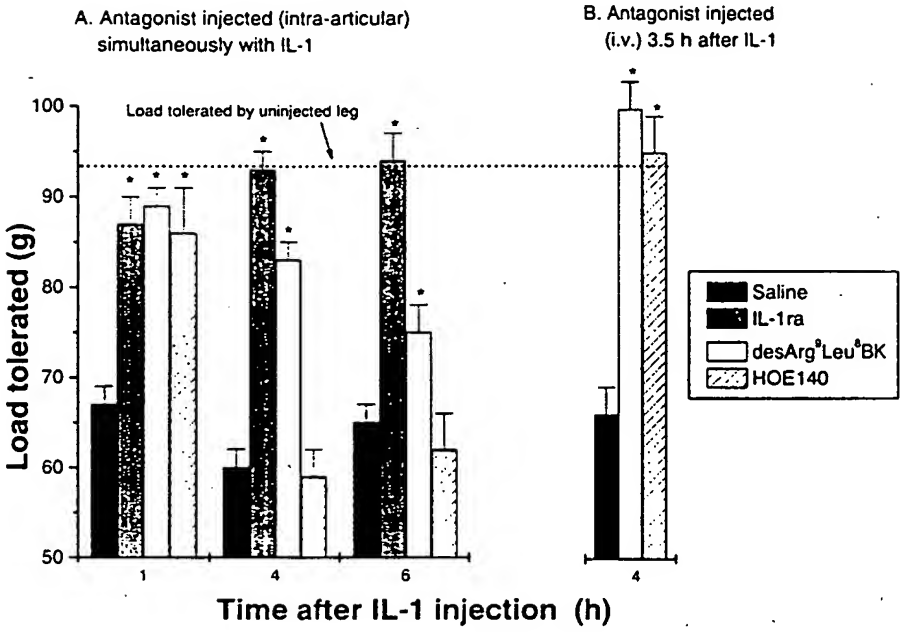

Fig. 4. Prevention and reversal of hyperalgesia by bradykinin antagonists in the rat knee joint. **A.** Hyperalgesia was induced by injection of IL-1β (1 U) together with saline, IL-1 receptor antagonist (IL-1ra, 100 ng), [desArg^9,Leu^8]-bradykinin (500 pmol), or HOE140 (5 pmol). The injection volume in all cases was 50 ml. Measurements of hyperalgesia were made one, four, and six hours after the injection. The saline controls (black columns) show that the hyperalgesia normally lasted for six hours. IL-1ra (gray columns) or the B_1 receptor antagonist (white columns) inhibited the hyperalgesia completely or partially at all three time points, whereas the B_2 receptor antagonist was effective only at the one-hour time point. **B.** Joints were injected with IL-1β as in (A). Antagonists ([desArg^9,Leu^8]-bradykinin, 10 nmol/kg, or HOE140, 0.1 nmol/kg) were injected intravenously 3.5 hours later, 30 minutes before the measurements were made. Either antagonist was able fully to reverse the IL-1-induced hyperalgesia. Values are mean ± SEM, n = 8. Values different from the saline controls ($P < 0.05$) are marked with asterisks (data from Davis and Perkins 1994b).

was able to enhance leukocyte accumulation, a response not seen in animals not pretreated with IL-1β.

Hyperalgesia can also be caused by injection of substance P (SP) into the knee joint (Davis and Perkins 1996), and surprisingly, is also prevented by IL-1ra, which implicates IL-1 in the mechanism. The source of this IL-1 is not known, but NK-1 receptors are known to occur on many types of inflammatory cell, so it is reasonable to postulate that these cells may release cytokines in response to activation of NK-1 receptors, as has been described in other systems (Okamoto et al. 1993; Manske et al. 1995). In contrast to

the results obtained when IL-1 was injected directly, however, co-injection of bradykinin antagonists with SP blocked the hyperalgesia only transiently; the long-lasting effect of the B_1-receptor antagonist was not seen. Furthermore, once the hyperalgesia was established, it could be reversed by systemic administration of a B_2-, but not a B_1-receptor antagonist. Thus, the contribution of B_1 receptor activation to the development and maintenance of the hyperalgesic state is evidently less when SP is used to induce hyperalgesia than when IL-1 is used, even though SP appears to be acting mainly through IL-1 production. Another difference was that indomethacin had no effect on SP-mediated hyperalgesia, which suggests that eicosanoids were not involved. This finding is consistent with the relatively smaller contribution of B_1 receptor activation to the hyperalgesia evoked by substance P than to that evoked by IL-1 or other inflammatory stimuli.

The major pathways that are postulated to account for the complex interactions between kinins, cytokines, and substance P in contributing to inflammatory hyperalgesia are summarized in Fig. 5. These are not, of course, the only mediators that are thought to be involved. Others, including nerve growth factor, opioid peptides, and catecholamines, are discussed elsewhere in this volume.

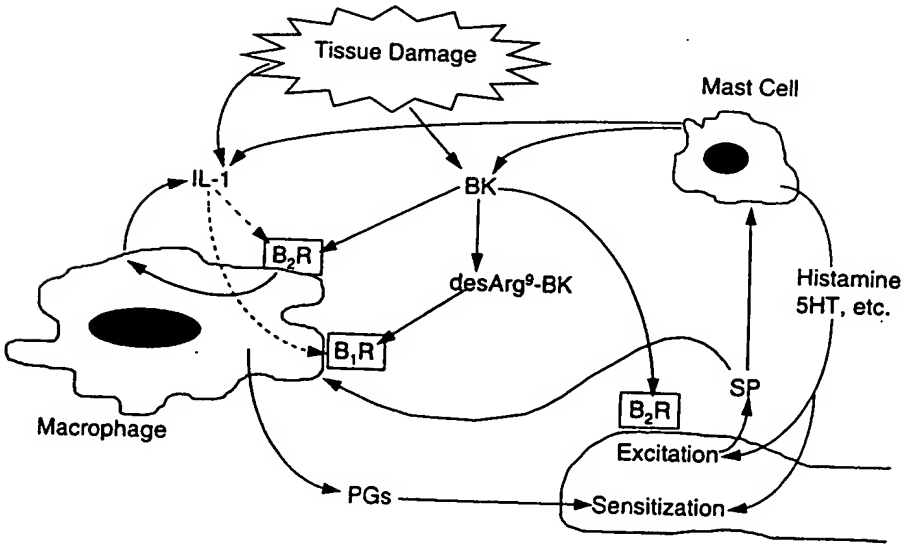

Fig. 5. Postulated interactions among cytokinins, kinins, and substance P in the generation of inflammatory hyperalgesia. Dotted arrows indicate the increased expression of kinin receptors induced by IL-1. BK = bradykinin; B_1R, B_2R = kinin receptors; SP = substance P; PGs = prostaglandins.

EFFECTS OF THE KININ SYSTEM IN THE SPINAL CORD AND BRAIN

The discussion thus far has focused on the potential role of bradykinin as a peripheral mediator contributing to inflammatory hyperalgesia. There is now increasing evidence that the kinin system may also play a role in the central nervous system (Walker et al. 1995b). All the components of the kinin system—kininogens, kallikrein, and kinin receptors—occur in the brain and spinal cord, and indirect evidence suggests that they may play a role in regulating nociceptive transmission and in other kinds of pathophysiological disturbance.

Binding studies in the spinal cord (Steranka et al. 1988; Fujiwara et al. 1989; Swift et al. 1993; Lopes et al. 1995) show a high density of B_2 receptors in the dorsal horn, associated with the terminals of nociceptive afferent fibers. Intrathecal administration of bradykinin produces enhancement of nociceptive responses if its indirect antinociceptive effect is prevented by adrenoceptor antagonists (Laneuville et al. 1989). Electrophysiological recordings from the rat spinal cord in vitro showed that the ventral root reflex caused by noxious stimuli to the tail was enhanced by bradykinin (Dray et al. 1988), and that bradykinin itself caused depolarization of afferent nerve terminals in the dorsal horn (Dunn and Rang 1990). Furthermore, Chapman and Dickenson (1992) showed that intrathecal administration of the B_2 receptor antagonist HOE 140 inhibited the firing of dorsal horn neurons following the injection of formalin into a rat's paw. This inhibitory effect was confined to the second, delayed phase of the response, the transient initial response being unaffected. This finding suggested that a local action of bradykinin in the spinal cord was contributing to the nociceptive discharge, even though the injury was peripheral. One caveat concerning these experiments is that laminectomy was necessary, so that local inflammation of the spinal cord was presumably present. It has not yet been established whether bradykinin release in the spinal cord contributes to inflammatory hyperalgesia under more physiological conditions. A clue as to the mechanism by which bradykinin might be acting to enhance nociceptive transmission came from in vitro studies on the release of the sensory neuropeptide, calcitonin gene-related peptide (CGRP), from the dorsal horn in response to electrical stimulation of the dorsal roots (Andreeva and Rang 1993), which showed that bradykinin applied to the spinal cord caused a marked increase in the amount of CGRP released, an effect blocked by B_2-receptor antagonists or by cyclooxygenase inhibitors.

In addition to this suggestive evidence for a role of bradykinin in modulating nociceptive transmission in the spinal cord, preliminary evidence suggests

that it may also have significant actions at higher levels. The concept of "illness-induced hyperalgesia" was developed (Watkins et al. 1995) to account for the fact that injection of cytokine-releasing agents, such as bacterial lipopolysaccharide (LPS), which causes fever and other signs of systemic illness, also results in a pronounced hyperalgesia, which is associated with synaptic facilitation in the spinal cord and elsewhere. Walker et al (1995a; 1996a) showed that the hyperalgesia produced by injection of LPS into the cerebral ventricles of rats could be blocked by local administration of HOE140 into the cerebral ventricles, but not by HOE140 given intravenously, which implicates central B_2 receptors in the mechanism. In this study, a B_1-receptor antagonist was ineffective when given concomitantly with LPS into the cerebral ventricles, which suggests that in this model the situation differs from that of hyperalgesia caused by peripheral inflammation, in which B_1 receptors play an important part (see above). However, in contrast, a similar study where LPS was administered peripherally with kinin antagonists administered into the lateral ventricles showed that the B_1 receptor antagonist [desArg^9, Leu^8]-bradykinin could prevent the LPS-induced hyperthermia when injected 2.5 hours after the LPS (Pela et al. 1995). In addition, in that study, [desArg^9]-bradykinin produced fever when injected into the lateral ventricles 24 hours after LPS treatment. Thus, it is possible that induction of B_1 receptors occurs in the CNS following inflammation, but only after a longer delay than is the case in the periphery.

SUMMARY AND CONCLUSIONS

The functioning of the kinin system is potentially complex for several reasons. There are two distinct types of kinin receptor, B_1 and B_2; the B_1 type is unusual in that its expression is strongly induced by cytokines, and probably also by other factors. Splice variants of these receptors may result in further diversity. Two endogenous kinins, bradykinin and kallidin, produced from different precursors, are selective for B_2 receptors; these give rise to two derivative kinins (the [desArg] derivatives of bradykinin and kallidin) that are selective for B_1 receptors. Functional levels of the various kinins are controlled by a variety of proteases and peptidases, some of which are known to be regulated by pathophysiological events in the tissues. Though we are beginning to understand more clearly the role of the two receptor types, mainly through the use of specific antagonists, little is known about the way in which the production, degradation, and interconversion of the various kinin mediators is controlled. Studies with antagonists show that bradykinin acting in the periphery plays an important role in inflammatory

hyperalgesia. In the early stages of inflammation, neuronally located B_2 receptors play the major role, but at a later stage, probably as a result of cytokine-mediated up-regulation of non-neuronal B_1 receptors, these become important in maintaining the hyperalgesia, probably by stimulating the release of other mediators, especially prostanoids, which act directly on sensory neurons. Bradykinin may also act at the level of the spinal cord and brain to produce hyperalgesia by facilitating transmission. In the spinal cord, it is able to enhance neuropeptide release, but it is not yet clear whether this mechanism operates under pathophysiological conditions in the whole animal. In the brain, bradykinin release appears to be one mechanism by which intracerebral LPS (a model for "illness-related hyperalgesia") enhances nociceptive transmission. The increasing evidence for an important role of kinins in the mechanism of inflammatory hyperalgesia suggests that bradykinin antagonists may, in the future, prove useful in pain management in the clinic.

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